# The Postprandial State and Risk of Cardiovascular Disease

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**Metabolism in man is regulated by complex hormonal signals and substrate interactions, and for many years the clinical focus has centred on the metabolic and hormonal picture after an overnight fast. More recently, the postprandial state, i.e. 'the period that comprises and follows a meal', has received more attention. The oral glucose tolerance test (OGTT), although highly non-physiological, has been used largely as a model of the postprandial state. Epidemiological studies have shown that, when 'impaired', oral glucose tolerance is associated with an increased risk of cardiovascular disease. Postprandial hyperlipidaemia has been investigated more recently in epidemiological, mechanistical and intervention studies, most of which indicate that high postprandial triglyceride levels, and particularly postprandial rich triglyceride remnants, constitute an increased risk for cardiovascular disease. Recent studies have shown that excessive postprandial glucose excursions are accompanied by oxidative stress and, less well known, activation of blood coagulation (increase in circulating D-dimers and prothrombin fragments). The mechanisms through which increased postprandial glucose levels and lipid concentrations may damage endothelial cells on blood vessel walls appear to be complex. These mechanisms include the activation of protein kinase C, increased expression of adhesion molecules, increased adhesion and uptake of leucocytes, increased production of proliferative substances such as endothelin, increased proliferation of endothelial cells, increased synthesis of collagen IV and fibronectin, and decreased production of nitric oxide (NO). In conclusion, the 'postprandial state' cumulatively covers almost half of the nycthemeral period, and its physiology involves numerous finely regulated motor, secretory, hormonal and metabolic events. Epidemiological and mechanistical studies have suggested that perturbations of the postprandial state are involved in cardiovascular disease. Correcting the abnormalities of the postprandial state must form part of the strategy for the prevention and management of cardiovascular diseases, particularly those that are associated with diabetes mellitus.**


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## Introduction

Metabolism in humans is regulated by precise hormonal signals and metabolic interactions. For many years, clinical studies have focused on hormonal and metabolic pathways under fasting conditions. Fasting plasma glucose remains the key element for the diagnosis of diabetes[1] and textbooks recommend a 12–14 hour fast before the collection of blood for lipid determination.[2] However, the postprandial state, i.e. 'the period that comprises and follows a meal', has more recently received increased attention. The duration of the postprandial state depends on the nature of the meal: after a meal consisting mainly of carbohydrates, the return to the basal state occurs within 2–3 hours; after a mixed meal it takes 3–5 hours; and after a fat-rich meal the return to the basal state may take as long as 8–10 hours.[3] The oral glucose tolerance test (OGTT), although highly non-physiological,[4] has been used mostly as a model of postprandial state, while fat tolerance tests have been introduced more recently. In this concise review, epidemiological data are surveyed that indicate that impaired glucose tolerance and excessive postprandial lipidaemia represent an increased risk for cardiovascular disease, and the proposed mechanisms involved in this effect are summarized.

## Epidemiological Evidence

### *Postprandial Hyperglycaemia*

The OGTT has been used mostly in epidemiological studies that attempt to evaluate the risk of cardiovascular disease. The main advantage of the OGTT is its simplicity: a single plasma glucose measurement 2 hours after a glucose load determines whether glucose tolerance is normal, impaired or indicates overt diabetes. The caveats of the OGTT are numerous because 75 or 100 g glucose

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is almost never ingested during a meal and, more importantly, many events associated with ingesting a pure glucose solution do not incorporate the numerous metabolic events associated with eating a mixed meal (Table 1).

Impaired glucose tolerance (IGT), as defined by the World Health Organization (WHO)[5] has been found to be a risk factor for cardiovascular disease in numerous investigations. For example, the prevalence of arterial hypertension is higher in Japanese men,[6] and in Finnish men and women with IGT[7] than in patients with normal glucose tolerance. In a study by Yamasaki *et al.*,[8] the prevalence of increased intimal wall thickness of the carotid artery was higher in patients with IGT. Increased prevalence of cardiovascular disease in subjects with IGT has been found in various populations, e.g. Chinese people,[9] non-Hispanic men and women,[10] and elderly Finnish men.[11] However, in Hispanic men and women,[10] and in elderly American people[12] with IGT, an increased prevalence of cardiovascular disease was not observed. These results indicate that ethnicity may be an important factor in determining the exact role that IGT plays in cardiovascular disease.[13]

Prospective studies investigating the risk of cardiovascular disease in patients with IGT have produced ambiguous results,[13] e.g. in the Paris Prospective Study, Fontbonne *et al.*,[14] observed that the blood glucose levels at 2 hours in the OGTT predicted the development of cardiovascular disease in men but this parameter was not statistically significant after adjustment for plasma insulin levels. Similarly, in the Helsinki Policemen Study,[15] 1-hour and 2-hour blood glucose levels in the OGTT predicted cardiovascular disease in univariate but not in multivariate analyses. Balkau *et al.*,[16] have recently reviewed the 20-year mortality in the Whitehall Study ($n$ = 10 025), the Paris Prospective Study ($n$ = 6629) and the Helsinki Policeman Study ($n$ = 631); their analyses of these three European cohorts have shown that high blood glucose levels, both fasting and 2 h in an OGTT, are statistical risk factors for mortality in these middle-aged non-diabetic men. In the Diabetes Intervention Study (DIS), 635 men and 504 women with newly diagnosed Type 2 diabetes were followed up for 11 years; multivariate analysis showed that postprandial blood glucose (but not fasting blood glucose) was a good predictive factor for myocardial infarction and atherosclerosis.[17]

After analysis of the epidemiological data, we concur with the conclusions presented recently by Haffner regarding cardiovascular disease and IGT,[13] i.e. there is evidence that cardiovascular risk factors are increased in subjects with IGT and the prevalence of cardiovascular disease is probably increased in IGT, particularly in middle-aged patients. However, evidence that suggests the incidence of cardiovascular disease is increased in subjects with IGT is insufficient at present. In patients with diabetes, the DIS suggests that postprandial blood glucose is a good predictive factor for cardiovascular disease.[17]

## *Postprandial Lipidaemia*

Almost 20 years ago, Zilversmit[18] suggested that atherogenesis was a postprandial phenomenon. Indeed, several studies support this contention including Ryu *et al.*,[19] who reported a significant relationship between postprandial plasma triglyceride concentration and the thickness of the carotid artery wall investigated by B-mode ultrasonography. In contrast, Syvänne *et al.*,[20] reported that the levels of atherogenic postprandial remnant lipoproteins, although increased in patients with Type 2 diabetes compared with controls, were not different in diabetic patients with or without coronary artery disease. Karpe *et al.*,[21] observed that the progress of angiographically-evaluated coronary artery disease in young males who survived a myocardial infarction was positively related to the postprandial level of small meal-derived chylomicron remnants.

Sharrett *et al.*,[22] using a test-meal, concluded that postprandial triglycerides represented an independent risk factor for carotid artery atherosclerosis in middle-aged men and women. Patsch *et al.*,[23] reported that 6- and 8-hour postprandial triglyceride levels had a high sensitivity and predictive power for coronary artery disease but, in direct contrast to the results of the DIS study in which fasting triglyceride levels demonstrated a good predictive value for myocardial infarction,[24] fasting triglyceride levels were only weak predictors of coronary artery disease. If dyslipidaemia is a recognized risk

Table 1. Advantages and caveats of the oral glucose tolerance test for assessing the postprandial state

| Advantages | Caveats |
|---|---|
| Simplicity | Highly non-physiological |
| Easy to standardize | Not representative of a 'normal meal' |
| Low cost | Does not elicit 'cephalic phase' insulin release |
| Precise cut-off points | Specific effects on gastric emptying |
| Extensive epidemiological data | Does not include digestion |
| | Poor reproducibility |



 

factor for cardiovascular disease,[25] the contribution of postprandial hyperlipidaemia to this risk, although suggested by various epidemiological studies, remains to be firmly established.

## Mechanisms Involved

The mechanisms by which excessive postprandial glucose and lipid levels may favour cardiovascular disease are numerous, complex and intricate. A few pathways are discussed here although a complete review has not been carried out.

### *Excessive Postprandial Glucose can be Toxic*

Excessive postprandial glucose levels lead to increased protein glycation, e.g. reflected by $HbA_{1c}$ concentrations, which increase 1–1.5 % when glucose tolerance is impaired.[26] Gerstein[27] proposed in a recent review that 'protein glycation in turn may promote cardiovascular disease through numerous mechanisms: glycated red cell membranes are less deformable; glycated low-density lipoprotein (LDL) apoproteins are poorly recognized by LDL receptors (leading to increased LDL uptake through scavenger pathways and increased foam cell formation), are more susceptible to oxidation and stimulate platelet aggregation; glycated high-density lipoprotein (HDL) is less able to transport cholesterol and glycated fibrin, and platelet membranes adversely affect vascular homeostasis. Furthermore, hyperglycaemia favours the formation of advanced glycation end-products whose accumulation may promote atherosclerosis through their effects on vessel walls, vessel matrices and endothelial dysfunction'.

### *Excessive Postprandial Glucose Levels Generate Oxidative Stress*

Ceriello[28] suggested recently that acute increases in plasma glucose levels may increase free radical production via at least three different routes (labile glycation, glucose autoxidation and intracellular activation of the polyol pathway). Furthermore, free radicals have been suggested to be involved in arterial hypertension[29] and potentially atherogenesis.[30]

### *Excessive Postprandial Glucose Levels are Associated With Transient Hypercoagulation*

Excessive postprandial glucose levels in diabetic patients are accompanied by an increased release into the circulation of D-dimers (D-D) and prothrombin fragments 1 + 2 (F1 + 2). These two markers represent the principal breakdown fragment of fibrin and the amount of thrombin released in the circulation, respectively.[31] This observation confirms previous data that also suggests that hyperglycaemia may possibly activate thrombin formation[32] and, consequently, fibrinolysis.[33] Interestingly, the meal-induced rise in D-D and F1 + 2 is markedly reduced when postprandial glucose excursions are themselves reduced by the $\alpha$-glucosidase inhibitor acarbose.[31] Therefore, repetitive meal-induced excessive increases in blood glucose lead to repetitive coagulation activation. As emphasized by Ceriello *et al.*,[31] the impact of these coagulation activation episodes on atherosclerosis development and progression, and on the occurrence of a cardiovascular accident may be more important than was assumed previously.

### *Excessive Postprandial Lipidaemia: A Direct or Indirect Pathway for Atherogenesis?*

*In vitro* studies have suggested initially that the postprandial rich triglyceride remnants are directly atherogenic. More recently, however, exaggerated postprandial lipidaemia has been suggested to be caused by the competition between chylomicrons and circulating very low-density lipoproteins (VLDL) of hepatic origin for common removal mechanisms.[34] Since chylomicrons are a better substrate for lipoprotein-lipase than VLDL, an accumulation of VLDL will occur as a result of postprandial hyperchylomicronaemia, which would result in bouts of hypertriglyceridaemia. In this respect, chylomicrons may not be directly atherogenic but postprandial hyperlipidaemia would result in an 'atherogenic lipoprotein profile'.[34] Furthermore, a positive relationship has been found between high triglyceride levels and both elevated small dense LDL concentrations and low HDL cholesterol levels, two well-known atherogenic lipid abnormalities.[2,25]

### *The Endothelium is a Target of Damage in the Postprandial State*

Evidence exists that hyperglycaemia interferes with the activity and function of endothelial cells. In a recent review, Haller[35] suggested that hyperglycaemia activates protein-kinase C (PKC; particularly PKC$\alpha$) in endothelial cells. PKC activation appears to stimulate the expression of adhesion molecules, i.e. Intracellular Adhesion Molecule 1 (ICAM-1), on endothelial cells. Indeed, an increase in circulating ICAM-1 has been observed in the course of an OGTT.[36] ICAM-1 facilitates the adhesion and uptake of leucocytes into the endothelium and furthermore, a damaged endothelium will release a decreased amount of vasodilatating substances like nitric oxide (NO) or prostacyclin. In addition, hyperglycaemia favours the release by the endothelium of vasoconstrictive and proliferative agents such as endothelin and platelet-derived growth factor (PDGF). Through this dual mechanism, the function of the diabetic vessels is markedly shifted towards vasoconstriction (Figures 1 and 2).



 

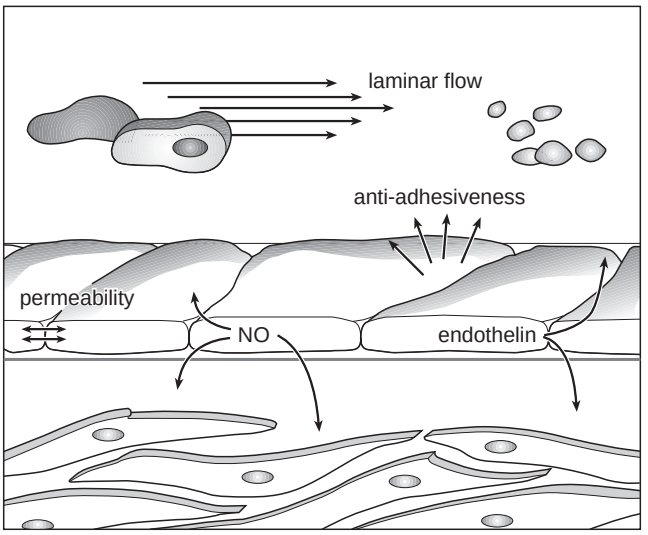


Figure 1. The endothelium releases nitric oxide (NO), which favours vasodilatation, while endothelin induces vasoconstriction. (From Haller [*Diabetic Medicine* 1997; **14**: S50–S56] with kind permission of the author and the copyright holder.)

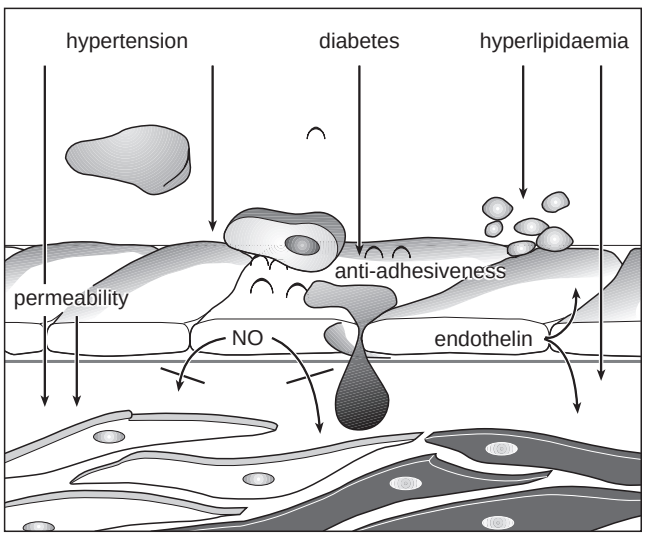


Figure 2. Arterial hypertension, diabetes and hyperlipidaemia damage the endothelial cells, and increase cell permeability and adhesiveness. The production of nitric oxide (NO) is impaired and production of endothelin is increased, which favours vasoconstriction and smooth-cell proliferation. (From Haller [*Diabetic Medicine* 1997; **14**: S50–S56] with kind permission of the author and the copyright holder.)

## Therapeutic Implications

### *Non-pharmacological Interventions may Help Reduce Postprandial Damage*

Lifestyle modifications may help reduce postprandial metabolic abnormalities and consequently postprandial damage. Modifications include a diet that is rich in fibre,[37] low in saturated fat and cholesterol,[38] rich in cis-monounsaturated fat (e.g. oleic acid [18:1])[39] and rich in natural antioxidants such as fruit, vegetables and, in moderation, red wine.[40,41] Restriction of total energy intake is also important in patients who are overweight or clinically obese.[42,43] Regular physical exercise is indicated to improve glucose tolerance and reduce the risk of progressing from IGT to Type 2 diabetes.[44] Moreover, a recent study has shown that prolonged walking beginning 1.5 h after the consumption of a fatty meal attenuates postprandial lipidaemia.[45] Smoking is associated with insulin resistance and lipid intolerance with an impaired triglyceride clearance after a mixed meal; interestingly, such lipid intolerance is not mirrored by fasting hypertriglyceridaemia.[46] These findings suggest that the cessation of smoking may be beneficial not only on insulin sensitivity[47,48] but also in terms of postprandial hyperlipidaemia.

### *Pharmacological Interventions*

As postprandial hyperglycaemia and hyperlipidaemia may contribute to an increased risk of cardiovascular disease, and because non-pharmacological interventions, such as diet and exercise, do not always succeed in reducing postprandial damage, pharmacological interventions may be considered as potential adjuvant therapies. In diabetic patients, the use of short-acting insulin or new rapidly acting antidiabetic agents may help to improve the control of postprandial glucose excursions. Furthermore, drugs that decrease the rate of gastric emptying or that interfere with substrate digestion and absorption by the intestinal tract are now considered. Several drugs that can delay gastric emptying are under development currently, e.g. GLP-1 and amylin derivatives (pramlintide), and have demonstrated the capacity to reduce postprandial hyperglycaemia and hyperinsulinaemia.[49] Compounds that specifically inhibit intestinal enzymes that play a crucial role in carbohydrate or fat absorption are also under development. Alpha-glucosidase inhibitors, such as acarbose or miglitol, have been investigated widely and work by reducing postprandial hyperglycaemia and hyperinsulinaemia without markedly affecting fasting glucose levels. In some studies, $\alpha$-glucosidase inhibitors have also been shown to reduce postprandial hypertriglyceridaemia.[50,51] Intestinal lipase inhibitors, such as orlistat, are being developed currently for the treatment of obesity and may also exert favourable effects on lipid profiles.[52] Further studies should demonstrate the long-term beneficial effects of such pharmacological interventions in reducing the risk of cardiovascular disease.

## Conclusions

The 'postprandial state' cumulatively includes approximately half of the nycthemeral period and involves numerous finely regulated motor, secretory, hormonal and metabolic events. Epidemiological and mechanistical studies have suggested that perturbations of the postprandial state are involved in cardiovascular disease. Cor-

recting the abnormalities of the postprandial state must form part of the strategy for preventing and managing cardiovascular diseases, particularly those that are associated with diabetes mellitus.

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